REMARKS

Claims 69-78 are pending. Claims 69-78 have been rejected. Specifically, rejections are levied under 35 U.S.C. Section 112, first paragraph (written description), Section 112, first paragraph (enablement), Section 112, second paragraph (indefiniteness), Section 102, and Section 103.

By this amendment, claims 69-72, 74 and 75 have been amended without prejudice or disclaimer and new claims 79, 80, and 81 have been added. Thus, claims 69-81 are currently under consideration.

Attached hereto is a marked up version of the changes made to the specification by the current amendment with additions underlined and deletions bracketed. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Support for the amended and new claims are found in the previously pending claims and the specification, for example at page 10, lines 24-26, page 2, lines 27-28 (autoimmune antigen and allergan). "Non-tumor" hematopoietic cells are implicitly disclosed by the cells exemplified in Example V of the specification (see page 42 et seq) which are bone marrow progenitor cells obtained from Balb/c mice. "[U]pon introduction to the individual" is supported by claim 69 as previously pending and additionally, e.g., in Example V of the specification. Applicants note that claims similar to new claims 80 and 81 have been previously rejected as allegedly indefinite. Applicants request reconsideration of the previous rejection, in view of the new Office policy on indefiniteness, as explained in "The Advance notice of changes to MPEP § 2173.02"[1].

In the present Office Action the following outstanding rejections have been withdrawn: the rejection of claims 52-68 under Section 112, 2d paragraph, the rejection of claims 52-55, 58, and 65-68 as allegedly anticipated by Zanetti (US Patent No. 5,508,386), the rejection of claims 52-55 as allegedly anticipated by the Romet-Lemonne reference, and the rejections of claims 52-

[1] "Advance notice of changes to MPEP § 2173.02 clarifying Office policy with respect to rejections made under 35 U.S.C. § 112, second paragraph in view of the Supreme Court holding in *Festo Corp.* . ." Memorandum from Stephen Kunin to the Patent Examining Corp. dated January 17, 2003).

55, 58 and 62-68 as allegedly obvious over Zanetti in view of various GenBank records, or allegedly obvious over Zambidis in view of Chambers and Zanetti.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Interview

Applicants wish to thank the Examiner and his supervisor for the courtesy of granting an interview to Applicants' representatives on April 9, 2003, with SPE George Elliott. The results of the interview are reflected in this response.

Rejections under 35 USC § 112, first paragraph (written description)

Claim 75

Claim 75 is rejected under 35 USC § 112, first paragraph on the ground that the term "transduced" is allegedly new matter (Office Action, page 3). Applicants respectively traverse this rejection. Claim 75 has been amended as suggested by the Examiners during the interview, and no longer recites the term transduced. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 69-78

Claims 69-78 are rejected for failure to satisfy the written description requirement of Section 112, first paragraph. Applicants respectfully traverse this rejection.

As discussed during the interview, the present application discloses pharmaceutical compositions comprising a nontumor lymphoid cell or non-tumor hematopoietic cell suitable for introduction into an individual and a pharmaceutically acceptable excipient, wherein said cell contains a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said

fusion protein comprising (1) an immunoglobulin heavy chain or light chain; and (2) a polypeptide containing at least one epitope of the antigen, wherein upon introduction to the individual said composition induces tolerance to the antigen in the individual.

As discussed in the interview, and further summarized below, Applicants respectfully submit that the specification provides an adequate written description of the claimed compositions and provide the following arguments in response to the rejection:

- the Office Action mischaracterizes the cited references;
- the specification describes the presently claimed pharmaceutical compositions;
- Suitable antigens are disclosed in the specification;
- The claimed pharmaceutical compositions are described and exemplified in the specification.
- Applicants will address the remarks relating to the Declarations of David Scott in the discussion of the enablement rejection, below.

The Office Action mischaracterizes the cited references

Applicants respectfully submit that the cited references are mischaracterized in the Office Action. The Office Action cites the Dal Porto, Vie, Arulanandam, Sekigawa, and Zwirner references as allegedly disclosing that "the art at the time of filing taught cells encoding numerous fusion proteins that are equivalent to the fusion protein required in the claims," and further that the "fusion protein[s] induced an immune response and did not induce tolerance." The Office Action states that tumor cells are disclosed in these references, but states that "the teachings of these references correlate to the claimed invention because their fusion proteins are equivalent to the fusion protein required by the claims." The Office Action also discusses the Zambidis (1993) abstract, which is stated to disclose a fusion immunoglobulin that induces tolerance, and a Zambidis (1996) publication which published after the filing date of the present application.

As discussed at the interview, Applicants respectfully disagree with the factual characterization of the cited references. In particular, none of the cited references disclose experiments relating to induction of an immune response or tolerance induction. Induction of an immune response is not suggested in any of the references. And the in vitro experimentation disclosed in each of these references does not provide information relating to the induction of tolerance in vivo as required by the present claims. Applicants will discuss these references in turn.

Dal Porto

Dal Porto teaches the use of J558L tumor cells as a factory for production of a fusion protein comprising a soluble divalent class I MHC molecule. The fusion protein was isolated, and used in in vitro studies on the interaction of the fusion protein with an alloreactive T cell clone.

Vie

In Vie, the nucleic acid encoding the fusion protein (Ig-IL2) was expressed in Cos and CHO cells, not J558L cells as asserted in the Office Action. The fusion protein in the supernatant was tested in vitro for ability to promote the growth of IL-2-dependent or lectin activated lymphocytes.

Arunlanandam

Fusion protein (Ig-CD2) was expressed in isolated CHO cells (not lymphoid cell lines as asserted in the Office Action) to improve avidity of CD2 interaction with its ligand. The fusion protein was then tested in vitro against hematopoietic cell lines.

Sekigawa

The ability of recombinant CD4 and CD4-IgG fusion protein to inhibit syncytium formation between HIV-infected and uninfected cells was tested. Sekigawa uses a fusion protein (CD4-Ig) but does not disclose a lymphoid cell transfected with DNA encoding a CD4-IgG fusion protein, as stated by the Examiner. By contrast, the only lymphoid cells used by Sekigawa are the T cells used in the in vitro syncytium test.

Zwirner

Zwirner uses the mouse B cell lymphoma line, A20. A MHC Class II I-E molecule is created by replacing the N-terminal domain with the variable regions of the antibody. Zwirner's construct does not have an Ig heavy chain or light chain, as required by the present claims. Zwirner seeks to design specificity of MHC using MAD light chains. Specificity is tested in vitro.

Zambidis (1993) abstract

Zambidis (1993) discloses preparation of a fusion protein using J558L tumor cells. The fusion protein is isolated, and use of the fusion protein, not cells, is suggested for in vivo and in vitro tolerance studies.

Zambidis (1996) PNAS publication

Applicants note that this publication is the work of the present inventors published in 1996, well after the filing date of the present application. As such, Applicants submit that this publication is not relevant to the state of the art at the time of filing of the present application.

In summary, Applicants respectfully submit that the references cited in the Office Action have been factually mischaracterized. As explained above, and at the interview, none of the cited references discloses testing for induction of a immune response, contrary to the Examiner's assertion. None of the cited references disclose cells that are "equivalent" to the presently claimed cells. Tolerance induction is not tested, and with the exception of the Zambidis abstract, none of the references even suggest tolerance experiments. Accordingly, Applicants respectfully submit that the cited references have no bearing on the written description or enablement of the present claims.

The specification fully describes the claimed pharmaceutical compositions

Applicants respectfully submit that the specification provides an adequate written description of the claimed compositions. For the convenience of the Examiner, Applicants provide the page and line numbers in the present specification where support for the presently claimed invention may be found.

Suitable antigens are described in the specification

The specification extensively describes antigens that are suitable for expression in the cells of the present invention. For example, the specification states:

> [s]uitable antigens are those that it would be desirable to induce and maintain immunological unresponsiveness to the epitope and/or antigen containing the epitope. Such antigens include pollen, ragweed, dustmites, and other known allergens. Suitable antigens also include autoantigens such as clotting factor VIII, acetocholine receptors, collagen, myelin basic protein, thyroglobulin, and histocompatability antigens. (Specification at page 10, lines 21-30)

Selection of epitopes is extensively described at page 10, line 21 to page 13, line 2. For example, the specification teaches, for example beginning at page 9, line 32 through to page 12, line 11, that an epitope of an antigen can be obtained and prepared by standard methods. The disclosure provides examples of antigen E of ragweed pollen, which was known in the art (Rafner *et al.* and Kuo *et al.*, each as cited at page 10, lines 12-15). Epitopes of antigen E have been identified (Olson *et al.* and Bond *et al.*, each as cited at page 10, lines 15-17). The disclosure further teaches that one of ordinary skill could identify DNA sequences encoding other antigens by searching databases, such as GenBank (see: page 10, lines 5-7). Also, the disclosure teaches that the amino acid of many of these antigens as well as epitopes of these antigens are known to those skilled in the art (see: page 10, lines 30-32). Further, the specification plainly states that the epitope and/or antigen can be a single epitope or it can be all or a portion of an antigen containing many epitopes, with an epitope interacting with T cells, or B cells or both (see: page 11, lines 1-10).

The specification also notes that the DNA sequence may code for *all* or part of an antigen. Specifically, the specification teaches that either one epitope of an antigen can be expressed in a fusion polypeptide or alternatively, an entire antigen can be expressed in a fusion polypeptide. For example, the specification states at page 11, lines 11-34:

> if tolerance is desired to a large and complex antigen, more than one epitope can be selected to be combined in a fusion immunoglobulin. Preferably, the entire antigen may be included in the fusion immunoglobulin [lines 16-20]. . . . [I]f there is little or no information known about epitopes of the antigen, it may be desirable to include the entire antigen in the fusion immunoglobulin [lines 30-34].

Applicants note that pretesting of epitopes (or antigens comprising epitopes) for ability to induce tolerance, or "preselection" of epitope which are previously characterized as inducing tolerance, is not necessary for the practice of the invention (although such epitopes may certainly be used in the cells of the presently pending claims). Put another way, the presently claimed pharmaceutical compositions may comprise a cell comprising any epitope (or a full-length protein comprising one or more epitopes of an antigen), regardless of whether that epitope has previously been demonstrated to induce tolerance. In that regard, Applicants previously provided a list of exemplary amino acid and/or polynucleotide sequence encoding antigenic epitopes that were publicly available at the time of filing of the present application. See Appendix A of the Amendment filed May 9, 2000. These publications are accession records to the GenBank and PubMed databases of the National Institutes of Health ("NIH"). These publications disclose a number of amino acid sequences and/or nucleic acid sequences encoding antigenic epitopes that would have been known and available to the skilled artisan at the time of invention. Specifically, these publications recite sequences for antigens or antigenic epitopes of: pollen, ragweed, dust mites, clotting factor VIII, acetylcholine receptors, collagen, myelin basic protein, thyroglobulin, and histocompatibility antigen.

Vectors, pharmaceutical compositions and methods for making the cells are disclosed.

The specification also fully describes preparation (see, e.g., pages 12-15) and introduction of a vector encoding a fusion protein into suitable lymphoid or hematopoietic cells (see, e.g., Example IV at pages 40-41; 18, lines 3-8). A variety of vector configurations are described. *See id.* The specification also discloses pharmaceutical compositions (see, e.g., page

19, line 14 - page 23 line 30), and methods of transfecting cell with expression vectors and administering the cells to animals (see, e.g., page 28, line 25 to page 30, line 15).

Pharmaceutical compositions comprising lymphoid or hematopoietic cells are described and exemplified

The specification extensively describes the claimed pharmaceutical composition that induces tolerance to an antigen, said tolerogenic composition comprising a lymphoid or hematopoietic cell suitable for introduction into an individual and a pharmaceutically acceptable excipient as described herein.

For example, the specification states:

> Hematopoietic or lymphoid cells are stably transformed with a vector to provide transformed cells expressing the fusion immunoglobulin (Specification at page 3, lines 6-9),

and that

> [T]ransformed cells can also be introduced into animals for induction and maintenance of tolerance to the heterologous epitope expressed by the transformed cells or to an antigen containing the heterologous epitope (Specification at page 17, lines 20-23).

The specification further describes, for example, transformed cells that can be introduced into animals for induction of tolerance, and lists suitable cells for transformation, including lymphoid or hematopoietic cells and cells of B cell lineage (see, e.g., page 17, lines 20-35).

Finally, the Examples exemplify preparation of a pharmaceutical composition comprising bone marrow cells comprising a fusion protein containing the lambda 12-26 c1 epitope, and intravenous administration into mice. *See* Specification at pages 42-43. Induction of B cell tolerance to the lambda peptide is described in Example 3. As discussed in the interview and further below, the lambda 12-26 c1 peptide is an art-recognized model antigen, as explained on page 31, lines 7-20. As such, the Examples demonstrating tolerance induction to the lambda c1 epitope do correspond to the specification. Applicants note that the bone marrow cells described

in the Examples are non-tumor lymphoid cells, including cells of B cell lineage. The bone marrow cells also comprise non-tumor hematopoietic cells.

For the above-stated reasons, withdrawal of this rejection is respectfully requested.

Rejections under 35 USC § 112, first paragraph, (enablement)

Claims 69-78 are rejected under 35 U.S.C. Section 112, first paragraph, as allegedly lacking enablement. The Office Action states that the specification is enabling for a non-tumor lymphoid cell comprising DNA encoding a fusion protein operably linked to a promoter, wherein said fusion protein comprises bacteriophage lambda c1 peptide 12-26 and an IgG heavy chain, however, the Office Action alleges that the specification does not enable any person skilled in the art to make and/or use the invention commensurate in scope with these claims. The Office Action states that the first and second Declarations of David Scott were deemed unpersuasive on the ground that the declarations allegedly do not correlate to the disclosure as originally filed. Applicants respectfully traverse this rejection, and offer the following arguments, which will be discussed in turn:

- The pharmaceutical compositions of the invention are as described in the specification;
- We have previously provided information demonstrating that the sequence of known antigens and epitopes of antigens was available in GenBank at the time this application was filed;
- As discussed at the interview, the lambda 12-26 c1 peptide is an art-recognized model antigen, and the examples provided in the present application go to allergic disease;
- The experiments discussed in the first and second declaration of David Scott correlate to the specification and should be considered;
- The experiments discussed in the Declarations result in tolerance induction; and
- the newly cited references are factually mischaracterized in the Office Action, and are discussed above with respect to the indefiniteness rejection;

The specification discloses and enable the pharmaceutical compositions of the present claims

Applicants respectfully submit that the specification discloses and enables the claimed pharmaceutical compositions, as detailed in the last response (*see* Amendment filed June 20, 2002, pages 8-12). Briefly, the specification extensively teaches how to make and use the claimed invention. As noted in the last response, the specification describes how to prepare expression cassettes for the fusion proteins (e.g., pages 8-17). The specification further describe how to transform cells with the expression cassettes (e.g., pages 17-19), and describes suitable cells for the methods of the invention including lymphoid or hematopoietic cells, including cells of B cell lineage (see, e.g., page 17, lines 20-35; Example V). Exemplary antigenic polypeptides (including autoantigens and allergens) are described (see, e.g., page 10, line 21 to page 13, line 2), and the specification further teaches that the nucleotide sequences for antigens are available in the art and can be identified by searching in a database such as GenBank (e.g., page 10, lines 5-20). Furthermore, the specification describes how to select epitopes of the antigens, if desired, for inclusion in the fusion protein (see specification at page 11, lines 11-34, which describes the selection process for the epitopes). Five working examples are provided, as further discussed below. Accordingly, Applicants respectfully submit that the specification fully enables the presently pending claims.

The sequence of known antigens and epitopes of antigens were available in GenBank at the time this application was filed

As discussed at the interview, the polynucleotide sequences of a large number of known antigens and/or epitopes of antigens were known in the art at the time of filing. Applicants previously provided a list of the nucleotide and/or amino acid sequences encoding exemplary antigenic polypeptides that were available in the art at the time the application was filed.[2] *See*

[2] These records are representative examples of nucleotide sequences available in the art prior to the 1994 priority date of the instant invention, corresponding to pollens (e.g., rye grass and Kentucky blue grass), ragweed allergens (e.g., Amb a I.1 and Amb a I.2), dust mite allergens (e.g., Der pI and Der fII), human coagulation factor VIII, human acetylcholine receptor

Appendix A to the Amendment filed April 9, 2000. Applicants emphasized that these sequences are merely representative examples of such sequences available in the art prior to 1994 and that numerous other sequences of the claimed antigenic polypeptides were readily available to the ordinarily skilled artisan at the time of the invention.

The lambda epitope used in the Examples is an art-recognized model allergan; thus the Examples provided in the application go to allergic disease

As discussed in the interview and in the specification at page 31, lines 7-20, the lambda 12-26 c1 peptide is an art-recognized model antigen and would be considered a model allergan. As such, the Examples demonstrating tolerance induction to the lambda c1 epitope exemplify tolerance induction in a model for allergic disease. *See* Specification at pages 42-43.

The declarations of David Scott disclose experiments using the system as described in the specification

The presently pending claims are directed towards a pharmaceutical composition comprising said cells, wherein the composition induces tolerance to an individual. The experiments disclosed in the declarations use this system for tolerance induction.

As discussed during the interview, the Second Declaration of Dr. David W. Scott (paper 38), submitted June 20, 2002, as well as in the Declaration of Dr. David W. Scott submitted with the last Amendment (paper no. 35, filed September 21, 2001), describe preparation of pharmaceutical compositions comprising non-tumor lymphoid cell expressing six additional different fusion polypeptides, and tested their ability to induce tolerance when administered to a host individual. Induction of tolerance was observed in all six cases. Data discussed in the Declarations have been published in peer reviewed scientific journals. Applicants submit that the Declaration in combination with the specification indicate that the present claims are broadly enabled.

(muscarinic receptor HM4), human collagen Type I, human myelin basic protein, human thyroglobulin and human histocompatibility antigens (MHC antigens HLA-DR, -DQ and -DP).

As discussed at the interview, the experiments discussed in the Declarations use the guidance taught in the specification, in combination with art-recognized model systems for the study of autoimmune disease and/or allergic reaction.

For example, the specification and the Declaration describe preparation of fusion constructs comprising polynucleotides encoding antigenic polypeptides (including autoantigens and allergens); introduction of these constructs into non-tumor lymphoid cells (which include B cells); introduction into an animal of a pharmaceutical composition for inducing tolerance comprising (a) non-tumor lymphoid cells expressing a fusion polypeptide and (b) a pharmaceutically acceptable excipient; and methods for testing whether tolerance is induced using art recognized model systems for autoimmune disease and allergic reaction.

(A) Six fusion protein constructs were prepared

Specifically, the declarations describe nontumor lymphoid cells comprising fusion proteins comprising the following antigenic polypeptides:

(i) myelin basic protein - full-length protein;

(ii) glutamic acid decarboxylase (GAD65) - full-length protein;

(iii) insulin B chain - residues 9-23;

(iv) interreceptor retinal binding protein (IRBP) - residues 161-180;

(v) bacteriophage lambda c1 protein - full-length protein and 12-26 epitope; and

(vi) ovalbumin - full-length protein.

As discussed in the declarations, myelin basic protein, GAD65, the insulin B chain residue 9-23, and IRBP are antigens associated with autoimmune disease. Antigens associated with autoimmune disease (also called autoantigens) are described in the specification at, e.g., page 8, line 1; page 10, lines 24-25; page 11, lines 12-16. Myelin basic protein is specifically mentioned at page 10, line 27. As discussed in the Declarations and at the interview, the bacteriophage lambda c1 protein is a model antigen suitable for the study of tolerance induction to a foreign protein, and as such, is considered a model allergan. *See* specification at page 31, 7-20, describing why the lambda c1 protein is used for tolerance studies. Ovalbumin, as discussed

in the declaration, is an allergenic chicken protein and as such, is an allergan. Allergans (i.e., antigens associated with allergic reactions) are described in the specification at, e.g., page 8, line 1; page 10, lines 24-25; page 11, lines 12-16. The lambda c1 protein is described at, e.g., page 10 lines 28-30. Further, the Examples describe tolerance induction using the lambda 12-26 epitope as a model antigen.

The First Declaration of David Scott (filed September 21, 2001) demonstrates that a portion of an antigenic polypeptide may be used in the fusion protein, or that a full-length antigenic polypeptide may be included in the fusion protein. The specification also states that a portion of an antigenic protein or the entire protein may be included in the fusion protein. *See* specification at page 11, lines 11-34.

Each of these antigenic polypeptides (or portions thereof) was incorporated into an IgG fusion protein according to the teaching of the specification and the IgG fusion proteins were expressed on nontumor lymphoid cells, specifically B cells, also in accordance with the teaching of the specification. Specifically, the specification discloses design and construction of expression vectors, including suitable immunoglobulin sequences, at pages 8-17. The specification further describe how to transform cells with the expression cassettes (e.g., pages 17-19), and describes suitable cells for the methods of the invention including lymphoid or hematopoietic cells, including cells of B cell lineage (see, e.g., page 17, lines 20-35; Example V). Transduced B cells are specifically described at page 41, line 13 (*see also* page 17, lines 24-31, discussing non-tumor lymphoid and non-tumor hematopoietic cells, and cells of B-cell lineage, and Example V, exemplifying non-tumor lymphoid cells).

(B) *Pharmaceutical compositions comprising these cells was administered into mice*

The Declarations further describe that pharmaceutical compositions comprising (a) non-tumor lymphoid or hematopoietic cells, specifically B cells, expressing the IgG fusion proteins; and (b) a pharmaceutically acceptable excipient, were administered to various art-recognized animal models of disease, for example, the NOD mouse model of autoimune diabetes, the experimental allergic encephalitis (EAE) model for autoimmune disease, and the experimental

autoimmune uveitis mouse model. Pharmaceutical compositions (see, e.g., page 19, line 14 to page 23, line 30), as well as methods of transfecting cell with expression vectors and administering the cells to animals (see, e.g., page 28, line 25 to page 30, line 15) are described in the specification. The specification also discloses administration of a pharmaceutical composition comprising a non-tumor lymphoid cell comprising a fusion polypeptide, and a pharmaceutically acceptable excipient at, for example, Example V (pages 42-43).

(C) Induction of tolerance was demonstrated

The declarations also disclose that tolerance was induced. Induction of tolerance was evaluated by measuring a decrease in immunological responsiveness. Methods for measuring a decrease in immunological responsiveness are taught in the specification at, for example, page 22, line 26-page 23, line 13; Example 3. The specification further states that a 2- to 100-fold decrease in immunological responsiveness is considered tolerance. *See, e.g.,* specification at page 29, lines 29-32.

Accordingly, Applicants respectfully submit that the experiments in the declarations use pharmaceutical compositions for tolerance induction as disclosed in the specification, and as such, the declarations in conjunction with the specification demonstrate that the claims are fully enabled.

With respect to the Examiner's assertion that the Agarwal et al reference (200, J. Clin. Investig 106:245-252) "does not correlate to the disclosure as originally filed" on the ground that an IgG hypervariable region in the fusion protein was allegedly used in the fusion protein, Applicants cannot find reference to a "hypervariable region" in the construct of Agarwal. Applicants believe that the Examiner may be reviewing a different publication than the Agarwal paper submitted with the Declarations, as the Examiner cites pages 5019, and 5020. By contrast, the 2000 J. Clin. Invest. article which is found at pages 245-252. Applicants further note that the Agarwal fusion protein was prepared essentially as described in the present examples. Even so, Applicants note that the present specification describes a variety of vector configurations. *See, e.g.,* specification at page 12, line 13 to page 13, line 6.

With respect to the Examiner's remarks concerning the Kang (1999) PNAS article, Applicants note that the Kang (1999) reference is discussed and submitted in the declaration because Kang demonstrates that retroviral transfer of a gene encoding the full length lambda cI repressor protein fused to an IgG is an effective approach for inducing tolerance to epitopes of an antigen. As such, Applicants submit that the Kang data relates to the present specification.

The experiments discussed in the Declarations result in tolerance induction

The Office Action states that the declaration allegedly "does not correlate to the specification" on the ground that the experimental allergic encephalitis (EAE) model mice "still had EAE" and the NOD model animals "still had inflammation". Applicants respectfully submit that the experiments disclosed in the specification demonstrate induction of tolerance and that Examiner is improperly imposing a requirement that the declarations demonstrate *a complete lack* of immunological responsiveness (e.g. a complete lack of inflammation). By contrast, Applicants submit that the specification clearly states, and one of ordinary skill would agree, that a 2- to 100-fold decrease in immunological responsiveness is considered tolerance. *See, e.g.,* specification at page 29, lines 29-32. The experiments disclosed in the Declarations clearly demonstrate a 2- to 100-fold decrease in immunological responsiveness.

Moreover, in a similar case, the Federal Circuit held that evidence of a complete cure was not required to enable claims to a method of treating scalp baldness. *See In re Cortright*, 165 F3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999). In *Cortright*, the rejected claims were to methods of "treating scalp baldness with an antimicrobial to restore hair growth . . ." The Board rejected the claims as lacking enablement on the ground that the claim phrase "restore hair growth" required complete restoration of a full head of hair, and Applicant's disclosure disclosed that only "three times as much hair growth as two months earlier," "filling-in some," and "fuzz." The Federal Circuit reversed the Board, holding that the Board erred by requiring demonstration of restoration of a full head of hair (i.e., a complete cure). The Federal Circuit stated that evidence of a full head of hair was not required, and concluded that the Applicant's disclosure of "fuzz," "filling-in some," and "three times as much hair growth as two months earlier" was sufficient to

support enablement of the pending claims. Applicants submit that the declaration evidence showing a increase in immunological nonresponsiveness is similarly acceptable under the law, and that evidence of complete immunological unresponsiveness is not required to enable the present claims.

For the above stated reasons, Applicants respectfully request withdrawal of this rejection.

Rejections under 35 USC § 112, second paragraph

Claims 69-78 are rejected as allegedly indefinite. Various grounds for rejection are provided, which are discussed in turn below. Applicants respectfully traverse the rejection.

Claim 69

Claim 69 is rejected as allegedly indefinite for reciting "a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced". Applicants respectfully traverse this rejection.

Applicants respectfully submit that the scope of this phrase is clear, and that one of ordinary skill understand the meaning and scope of the phrase "at least one epitope of the antigen to which tolerance is desired to be induced", which was added to the claim based upon the suggestion of Examiner Reynolds during the Interview held April 17, 2002. However, to expedite prosecution, the claim has been amended to remove "to which tolerance is desired to be induced." Withdrawal of this rejection is respectfully requested.

Claim 70

Claim 70 is rejected as allegedly indefinite on the ground that nucleic acid sequences do not comprise vectors; rather vectors comprise nucleic acid sequences. Claim 70 has been amended and now recites that "said nucleic acid sequence is introduced into the cell in a viral vector". Support for the amendment is found in claim 70 as previously pending, and in the specification at, e.g., Example IV and page 17, line 6. Applicants believe that this amendment addresses the Examiner's concern, and withdrawal of this rejection is respectfully requested.

Claim 71

Claim 71 is rejected as allegedly indefinite on the ground that there should be a comma after "retroviral vector" to comply with standard Markush format. Applicants respectfully submit that this is a ground for, at best, an objection, not a statutory rejection.[3] However, to expedite prosecution, claim 71 has been amended to add the comma as suggested by the Examiner. Withdrawal of this rejection is respectfully requested.

Claim 72

Claim 72 is rejected as indefinite on the ground that it is allegedly unclear if any of the "two or more copies of the nucleic acid sequence" are the "nucleic acid sequence" in claim 69 or if the "two or more copies of the nucleic acid sequence" are in addition to the "nucleic acid sequence" in claim 69. To expedite prosecution, claim 72 has been amended and now states "two or more copies of the nucleic acid sequence encoding said fusion protein of claim 69" (emphasis added). Applicants submit that this amendment clarifies that the nucleic acid encoding the fusion protein is the nucleic acid sequence of claim 69. Withdrawal of this rejection is respectfully requested.

Claim 74

Claim 74 is rejected as allegedly indefinite on the ground that the phrase "polypeptide or portion thereof" lacks antecedent basis. Applicants thank the Examiner for pointing this out, and the claim has been amended to delete the phrase "or portion thereof" as suggested by the Examiner. Withdrawal of this rejection is respectfully requested.

Rejections under 35 USC § 102

Zanetti

Claim 69 is rejected under 35 USC 102(e) as allegedly being anticipated by Zanetti of record (US Patent 5,508,386, April 16, 1996). Applicants respectfully traverse this rejection.

[3] Applicants further note that the examples in the MPEP do not show a comma between the last two members of the exemplified Markush groups.

Claim 69 has been amended and now recite that the tolerogenic composition comprises "a non-tumor lymphoid cell or non-tumor hematopoietic cell. By contrast, Zanetti discloses J558L cell which are myeloma tumor cells. *See also* specification at page 36, lines 17-18 (stating that J558L cells are myeloma cells). Accordingly, Zanetti cannot anticipate the present claims which require non-tumor cells. At the interview, the Examiner agreed to withdraw this rejection if the claim was amended to recite nontumor cells. Accordingly, withdrawal of this rejection is respectfully requested.

Zambidis

Claim 69 is rejected under 35 USC 102(b) as allegedly being anticipated by Zambidis of record (Feb. 1, 1993, J. Cellular Biochem., Vol. 9, No. 17, Part B, page 251). Applicants respectfully traverse this rejection.

Claim 69 has been amended and now recite that the tolerogenic composition comprises "a non-tumor lymphoid cell or non-tumor hematopoietic cell. By contrast, Zambidis discloses J558L cell which are myeloma tumor cells. *See also* specification at page 36, lines 17-18 (stating that J558L cells are myeloma cells). Accordingly, Zambidis cannot anticipate the present claims which require non-tumor cells. At the interview, the Examiner agreed to withdraw this rejection if the claim was amended to recite a nontumor cell. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 USC § 103

Claims 69-78 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Chambers (Feb. 1992, PNAS, USA, Vol. 89, pages 1026-1030) in view of Zambidis (Feb. 1, 1993, J. Cellular Biochem., Vol. 9, No. 17, Part B, page 251). Chambers is cited as teaching peripheral blood lymphocytes (PBL) comprising a retroviral vector encoding the IL-6 protein. Zambidis is cited as teaching "a cell line transfected with a vector encoding a fusion protein comprising an IgG heavy chain and a bacteriophage lambda c1 protein on the N-terminus." The

Office Action relies upon three grounds for motivation to combine these references. Applicants respectfully traverse this rejection.

Legal standard for obviousness rejection

To establish a prima facie case of obviousness, three basic criteria must be met. First, the prior art reference(s) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicants' disclosure. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Moreover, under the law of obviousness, a showing of a suggestion, teaching, or motivation to combine prior teachings must be clear and particular. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Ct. 1999). Furthermore, the Court in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Ct. 1998), pointed out that when determining the patentability of a claimed invention which combines two known elements, the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.

Applicants respectfully submit that the Examiner has not demonstrated a suggestion or motivation to combine the references, nor has the Examiner shown that there is a reasonable expectation of success. In addition, Applicants respectfully submit that the Examiner has not demonstrated that each and every limitation of claim 77 is present in the cited references; accordingly, a *prima facie* case of obviousness has not been made for that claim.

The Office Action has not demonstrated a suggestion or motivation to combine the cited references

Applicants submit that one of skill in the art would not be motivated to combine the cited references. In particular, Applicants note that the Zambidis reference does not teach or suggest administration of non-tumor cells to an individual, wherein tolerance is induced in the individual. By contrast, Zambidis discloses J558L tumor cells which are used as a factory for the production of fusion protein. Zambidis does not demonstrate administration of the fusion

immunoglobulin, nor does Zambidis demonstrate that tolerance results following administration of the fusion protein. Instead, Zambidis merely discloses in vitro characterization of the fusion protein, and suggests that further experiments should be performed to test whether administration of a fusion protein will result in tolerance. This speculative disclosure regarding fusion proteins certainly does not provide motivation to modify Zambidis to (a) use the cells for administration, wherein tolerance induction results, rather than to use of cells as a factory for production of the fusion protein as disclosed in Zambidis; (b) substitute administration of the cells for the suggestion to administer the fusion protein as disclosed in Zambidis; and (c) substitute nontumor cells for the tumor cells disclosed in Zambidis.

Similarly, because the Zambidis reference does not teach or suggest administration of non-tumor cells to an individual wherein tolerance is induced in the individual, and because Zambidis only suggests, but does not demonstrate, that administration of fusion protein results in tolerance, one of ordinary skill would not have had a reasonable expectation of success.

The Office Action provided several grounds for motivation to combine the cited references. These are discussed in turn below.

(a) The Office Action states that "one of ordinary skill would be motivated to replace the tumor cells of Zambidis with the nontumor PBL of Chambers in order to prevent causing tumors in in vivo tolerance experiments as suggested by Zambidis." Applicants assume that that this motivation pertains to in vivo tolerance experiments involving the administration of cells, because tumor formation is not a concern when the isolated and purified fusion immunoglobulins are administered.

Applicants submit that this ground for motivation is improper and cannot form the basis for the obviousness rejection to the extent that it relies on an alleged disclosure of administration of cells in Zambidis. As noted above, Zambidis neither teaches nor suggests that the tumor cells (or indeed any cell) *can themselves be administered*. Instead, the experiments suggested in Zambidis concern administration of the fusion immunoglobulin, not administration of cells. The only cells disclosed in Zambidis are the J558L tumor cells, which are used as a factory for the

production of fusion protein (which is then purified and analyzed), and even the last sentence of Zambidis refers to in vivo and in vitro tolerance experiments *using the fusion protein itself,* not cells comprising a fusion protein. Accordingly, one of ordinary skill, reading Zambidis, would not contemplate administering the tumor cells of Zambidis, which are used solely to produce the fusion protein.[4]

Withdrawal of this rejection is respectfully requested.

(b) The Office Action also states that "one of skill in the art would have been motivated to replace the IL-6 of Chambers with the fusion protein of Zambidis to perform *in vivo* and *in vitro* tolerance experiments with this fusion protein as suggested by Zambidis." Applicants respectfully submit that one of skill in the art would not be motivated to use PBL for production of the fusion protein of Zambidis. Chambers uses a cytokine expression system in vivo, which is characterized to produce only minimal amounts of IL-6 product. (*See, e.g.*, Table 1, showing nanogram or sub-nanogram IL-6 production in vivo, and in vitro from cell lines). By contrast, the tumor cells of Zambidis were used as a factory to make relatively large amounts of fusion protein in vitro, such that fusion protein was isolated and purified for subsequent in vitro and in vivo characterization. Applicants respectfully submit that one of ordinary skill would not be motivated to replace the IL-6 of Chambers, which is characterized as being produced at minimal levels in vivo, with the fusion protein of Zambidis. Applicants respectfully request withdrawal of this rejection.

(c) The Office Action also states that "one of skill in the art would have been motivated to use a retroviral vector as taught by Chambers in the cell of Zambidis because retroviral vectors were the most efficient means of introducing genes into a variety of tissues". Applicants do not disagree that the retroviral vector of Chambers is useful for introduction of genes into lymphoid

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[4] Even assuming that one of skill would be motivated to prevent tumor formation as suggested in the Office Action (which Applicants do not concede), Applicants note that the cells of Chambers did cause tumors when administered to mice. Chambers notes that it is unclear why the cells caused tumors, and that the cause of the tumor formation was unknown. One of skill in the art, reading Chambers, would certainly not select the cells of Chambers to avoid tumor formation, when Chambers teaches that their cells inexplicably cause tumor formation.

and hematopoietic cells. In fact, the Chambers reference is cited in the present application as a suitable vector for the methods of the invention. However, the present claims are not rendered obvious by the inclusion of the vector of Chambers in the cell of Zambidis, because Zambidis teaches only tumor cells. The vector of Chambers does not remedy this deficit. Withdrawal of this rejection is respectfully requested.

For the above-stated reasons, withdrawal of this rejection is respectfully requested.

In addition, Applicants respectfully submit that a prima facie case of obviousness of claims 77 has not been made because each and every element of the claim is not taught or suggested in the cited references. PBL do not contain bone marrow cells, as required by claim 77. Bone marrow cells, by definition, are found in the bone marrow. By contrast, PBL (peripheral blood lymphocytes) are found in the periphery by definition. Accordingly, the rejection of claim 77 is improper because Chambers does not disclose bone marrow cells, and therefore each and every limitation of the claim is not taught or suggested by the cited references. Withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the fee transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 308072000110.

Respectfully submitted,

Dated: May 30, 2003

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the Claims

Please amend claims 69-72, 74 and 75 as follows.

69. (Amended) A pharmaceutical composition that induces tolerance to an antigen, said [tolerogenic] composition comprising a non-tumor lymphoid cell or non-tumor hematopoietic cell suitable for introduction into an individual and a pharmaceutically acceptable excipient, wherein said cell contains a nucleic acid sequence encoding a fusion protein operably linked to a promoter,

said fusion protein comprising (1) an immunoglobulin heavy chain or light chain; and (2) a polypeptide containing at least one epitope of the antigen [to which tolerance is desired to be induced];

wherein upon introduction to the individual said composition induces tolerance to the antigen in [an]the individual.

70. (Amended) The pharmaceutical composition of claim 69, wherein said nucleic acid sequence [comprises]was introduced into the cell in a viral vector.

71. (Amended) The pharmaceutical composition of claim 70, wherein said viral vector is selected from the group consisting of retroviral vector, and baculovirus vector.

72. (Amended) The pharmaceutical composition of claim 70, wherein there are two or more copies of the nucleic acid sequence encoding said fusion protein of claim 69 operatively linked to said promoter.

74. (Amended) The pharmaceutical composition of claim 70, wherein said fusion protein comprises an N-terminal variable region of said heavy chain and has said polypeptide [or

portion thereof]inserted adjacent to the first framework region of said N-terminal variable region.

75. (Amended) The pharmaceutical composition of claim 70, wherein the nucleic acid sequence is introduced by [transduction]a virus encoding the fusion protein.